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The importance of basidiomycetous fungi cultured from the sputum of chronic idiopathic cough: A study to determine the existence of recognizable clinical patterns to distinguish CIC from non-CIC

Haruhiko Ogawa [a,*], **Masaki Fujimura** [b], **Yasuo Takeuchi** [c], **Koichi Makimura** [d]

[a] *Division of Pulmonary Medicine, Ishikawa-ken Saiseikai Kanazawa Hospital, 13-6 ni Akatsuchi-machi, Kanazawa 920-0353, Japan*
[b] *Respiratory Medicine, Cellular Transplantation Biology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan*
[c] *Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagamihara National Hospital, Sagamihara, Japan*
[d] *Department of Molecular Biology and Gene Diagnosis, Institute of Medical Mycology and Genome Research Center, Graduate School of Medical Science, Teikyo University, Hachioji, Japan*

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Summary
Background: Recently we have reported 5 cases of allergic fungal cough (AFC), which is intractable and is characterized by sensitization to one of basidiomycetous fungus. Because AFC shows good clinical response to antifungal drugs, diagnosing AFC in patients with CIC may lead to the consequent management of CIC. Therefore, we determined the incidence of CIC among our hospital patients, and the frequency of BM fungi in sputum samples collected from patients with CIC. Furthermore we evaluated whether or not a recognizable clinical pattern that distinguishes CIC from non-CIC exists.
Methods: The medical records of 70 patients complaining of chronic cough who were referred to our hospital for diagnosis and treatment were analyzed retrospectively.
Results: The primary diagnoses were CIC (27.0%), cough-variant asthma (30.0%), atopic cough (24.3%), sinobronchial syndrome (8.6%), cough-predominant asthma (7.1%), gastro-esophageal reflux (1.4%), and others (1.4%). In CIC patients, the median age, proportion of females, and frequency of acute upper respiratory tract infection did not differ significantly from those in non-CIC patients. CIC patients had a longer median duration of cough (11.0 months vs. 3.5 months). The positive ratio of BM cultured from the sputa of CIC patients (62.5%) was significantly ($p = 0.0061$) higher than that of non-CIC patients (16.7%).

* Corresponding author. Tel.: +81 76 266 1060; fax: +81 76 266 1070.
E-mail address: saiseikh@po3.nsknet.or.jp (H. Ogawa).

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Conclusion: The existence of BM fungi in induced sputum may be an important factor for distinguishing the clinical manifestation of CIC from that of non-CIC. The clinical approach from the aspect of fungal allergy may serve as a clue that may aid in the successful management of CIC.

Introduction

Cough is the most common complaint for which medical attention is sought, and chronic cough can be both physically and mentally debilitating.

Despite extensive diagnostic evaluation and numerous treatment guidelines,[1–4] a number of patients remain troubled by chronic and uncontrollable cough. Chronic idiopathic cough (CIC)[5,6] has been reported as a subgroup of chronic coughers in whom a diagnosis cannot be made even after thorough systematic investigation. Even though the major causes of chronic cough exhibit geographical variation[7,8] it is important to investigate how to manage chronic intractable cough and how to address the problem of CIC and minimize the diagnosis of CIC.

Recently, we proposed a new clinical disease concept termed fungus-associated chronic cough (FACC),[9] which entailed the following manifestations: (1) chronic cough; (2) the presence of environmental fungi, particularly basidiomycetous (BM) fungi, in the sputum; and (3) good clinical response to antifungal drugs.

Our previous study has revealed that FACC includes another type of condition termed allergic fungal cough (AFC),[10] which is intractable and is characterized by sensitization with *Bjerkandera adusta* (*B. adusta)*, a type of basidiomycetous (BM) fungus.

Because AFC shows good clinical response to antifungal drugs, diagnosing AFC among patients diagnosed with CIC may become the first step for the successful management of chronic intractable cough patients, which will lead to the consequent management of CIC.

To assess the usefulness of diagnosing AFC in patients with CIC, we determined the incidence of CIC among our hospital patients, and the frequency of BM fungi in sputum samples collected from patients with CIC. Furthermore we evaluated whether or not a recognizable clinical pattern that distinguishes CIC from non-CIC exists.

Methods

Patients

The medical records of 70 patients referred to Saiseikai Kanazawa Hospital between June and December 2006 were collected and reviewed retrospectively. All patients had a cough of at least 8 week's duration. Their referrals were made not only by primary care physicians but also by respiratory specialists. The following information was collected from the medical records: name, date of birth, gender, source of referral, duration of symptoms, preceding acute upper respiratory tract infection (UTRI), smoking habits, and results of fungal culture obtained from nebulized hypertonic saline-induced sputum that was collected from the patients at their first visit.

The cause of chronic cough in each patient was diagnosed based on a questionnaire, blood examination findings, chest and sinus X-rays, induced-sputum examination, pulmonary function tests,[11] test for cough reflex sensitivity to inhaled capsaicin,[12] bronchial reversibility in response to bronchodilators, bronchial responsiveness to methacholine,[13] and the efficacy of individual cause-specific treatments.

Capsaicin cough threshold was measured as an index of airway cough reflex sensitivity according to the method reported by the authors.[12] The capsaicin cough threshold was defined as the lowest concentration of inhaled capsaicin eliciting five or more coughs. Positive bronchial reversibility was defined as percentage increase in FEV_1 >12% and absolute increase in FEV_1 >200 mL. The nonspecific bronchial responsiveness to methacholine was assessed according to the method described by Cockcroft et al.[13] The results were expressed as the provocation concentration (mg/mL) required to cause a 20% or more fall from the baseline FEV_1 (respiratory threshold of methacholine; RT-Meth).

The examinations were performed in accordance with the diagnostic criteria for each cause, as recommended by the Japanese Cough Research Society[1] and Japanese Respiratory Society.[2]

Diagnostic criteria of chronic cough

The clinical features of atopic cough (AC)[14–16] were considered to be as follows: (1) chronic bronchodilator-resistant nonproductive cough with ''tickle'' in the throat lasting for more than eight weeks; (2) absence of wheezing, dyspnea, hemoptysis, or pleurisy, and no adventitious lung sounds on physical examination; (3) presence of one or more global atopic findings, including past history and/or complication of allergic diseases except for bronchial asthma, family history of allergic diseases, peripheral blood eosinophilia, elevated total IgE level in the serum, positive specific IgE antibody to common aeroallergens, and positive allergen skin test; (4) presence of eosinophils in hypertonic saline-induced sputum and/or submucosa of biopsied trachea and/or bronchi; (5) normal limits of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio; (6) no bronchial reversibility defined as less than a 5% increase in FEV_1 after inhalation of 300 μg salbutamol following 250 mg aminophylline injection; (7) bronchial responsiveness within normal limits; (8) increased airway cough reflex sensitivity; and (9) complete relief of the cough upon treatment with histamine H1 antagonists, inhaled corticosteroid therapy and/or oral corticosteroid therapy.

Cough-variant asthma (CVA)[17] was diagnosed based on the following diagnostic criteria: (1) chronic nonproductive cough

as an isolated symptom lasting for more than eight weeks; (2) absence of a history of wheezing or dyspnea, and no adventitious lung sounds on physical examination; (3) absence of PND to account for the cough; (4) normal limits of FEV_1, FVC, and FEV_1/FVC ratio; (5) presence of bronchial hyper-responsiveness (RT-Meth $<$ 10 mg/mL); (6) normal limits of cough reflex sensitivity (C5 $>$ 3.9 μm); (7) no abnormal findings indicative of cough aetiology on chest radiograph; and (8) relief of cough with bronchodilator therapy. When all criteria were satisfied, a definite diagnosis of CVA was made.

The patient was diagnosed with cough-predominant asthma when the following criteria were satisfied: (1) chronic cough as a sole manifestation; (2) no history of wheezing or dyspnea attacks suggestive of asthma; (3) no adventitious lung sounds on lung auscultation; (4) relief from cough on bronchodilator therapy; and (5) presence of one or more of the following findings that are specific to bronchial asthma: (i) positive bronchial reversibility in response to beta-2 agonists defined as increases in FEV_1 of $>$12% and $>$200 mL following inhalation of 300 μg salbutamol sulfate and (ii) increased diurnal variation of peak flow rate. Some researchers may diagnose such conditions as cough-variant asthma whereas others, as bronchial asthma.

Sinobronchial syndrome (SBS)[18] was diagnosed according to the following diagnostic criteria: (1) productive cough without wheezing lasting for eight weeks or more; (2) one or more of the following findings: (i) symptoms such as post-nasal drip (PND) and throat clearing; (ii) signs such as mucus or mucopurulent secretion in the upper and middle pharynx, and cobble stone appearance of the mucosa; (iii) fluid retention or mucosal thickening on sinus X-ray or computed tomographic (CT) scan; and (iv) increased neutrophils without eosinophils in nasal secretions and spontaneous sputum; (3) no atopic findings; (4) no bronchial reversibility; (5) bronchial responsiveness within normal limits; (6) normal limits of cough reflex sensitivity; and (7) relief of cough on treatment with 14- or 15-member macrolides. The efficacy of the treatment was evaluated at 2 months after the start of treatment and was judged as effective when the productive cough diminished to half or less. When all criteria were satisfied, a definite diagnosis of SBS was made.

The specific treatments given before the diagnosis of CIC was made were as follows. Suspected CVA[17] was treated in the first instance with β2-agonists (a combination of oral 40 μg/d clenbuterol and 200 μg salbutamol inhalation at bedtime and on demand). If this proved insufficient, treatment was stepped up according to the guidelines on the treatment of asthma. Suspected AC,[13] i.e., bronchodilator-resistant cough (eosinophilic tracheobronchitis with cough hypersensitivity), was treated with histamine H1 antagonists and inhaled corticosteroids (a combination of 10 mg/d cetrizine hydrochloride and 400–800 μg/d fluticasone propionate). Suspected SBS[18] was treated with clarithromycin (oral 200 mg/d). Suspected GER[4] was treated with a high dose of proton-pump inhibitors. The duration of each treatment was a minimum of 3 months.

Mycological study

Induced-sputum samples obtained from the patients were inoculated on Sabouraud's dextrose agar (SDA) containing chloramphenicol. The morphological features of the strains were recorded by a mycological specialist by using the slide culture method (30 °C for 2 weeks) and by staining with lactophenol cotton blue.

Statistical analysis

Statistical analysis of quantitative data [age at referral, age at onset of cough, duration of cough, and logarithmic transformation of concentration causing 5 coughs (log C5)] was performed using the Mann–Whitney *U* test. Dichotomous data (gender, previous URTI, and positive result of cultured basidiomycetous BM fungi) were analyzed using a χ^2 test. A p value of less than 0.05 was considered to be statistically significant. The trial was approved by the institutional review boards, and informed consent was obtained from each of the 70 patients.

Results

Information was collected from a total of 70 consecutive new patient referrals between June and December 2006. The studied patients comprised 33 males and 37 females. The median age of the patients at referral was 51 years (range 22–80 years). The median duration of symptoms was 4.5 months (range 2–181 months). Chest X-rays were normal for all the patients and mucosal thickness or fluid collection of maxilla glands in sinus X-rays was detected in 6 patients. Nine patients were current smokers, and 14 patients were ex-smokers.

Chronic airflow limitation was considered present when the ratio of FEV_1 to FVC (FEV_1/FVC ratio) was $<$0.7. An FEV_1 of $<$80% of the predicted value was found in only three of the 70 patients. Cough reflex sensitivity was increased in 29 patients. Bronchial responsiveness to methacholine was exaggerated in five patients.

The bronchodilator therapy showed effectiveness in 26 patients (21 CVA patients and 5 cough-predominant asthma patients) but not in the other 44 patients. The therapy of histamine H1 antagonists and inhaled corticosteroids produced a clinical response in 17 patients with AC.

A cause for the cough was identified in 51 patients. In the remaining 19 patients, no cause was found and therefore a diagnosis of CIC was given. The primary diagnoses were CIC (27.1%), CVA (30.0%), AC (24.3%), SBS (8.6%), cough-predominant asthma (7.1%), GER (1.4%), and others (1.4%) (Table 1).

The characteristics of the 19 patients with CIC were compared with 51 patients with non-CIC in whom another diagnosis had been assigned (Table 2). The CIC patients had a median age of 59 years (range, 22–80 years), and 42.1% were female. The respective values for the non-CIC patients were 51 years (range, 22–78 years) and 56.9%. None of the characteristics were different between the 2 groups. The median duration of cough in the CIC group was 24 months (range, 8–180 months), which was longer compared with 12 months (range, 8–120 months) in the non-CIC group ($p = 0.0292$). The capsaicin challenge results were available for 19 CIC patients (100%) and 47 non-CIC patients (92.2%). A significant difference in the cough sensitivity was found between the 2 groups ($p = 0.0292$).

Table 1 Primary diagnosis of the causes of chronic cough.

Primary diagnosis			Number of patients
CIC			19
Non-CIC	Cough-variant asthma		21
	Atopic cough		17
	Sinobronchial syndrome		6
	Cough-predominant asthma		5
	Others	GER	1
		Psychogenic	1
Total			70

The frequencies of all fungi detected from the total of 34 patients are summarized in Table 3a. Positive results of the sputum culture for BM were obtained in 10 of the 16 CIC patients (62.5%) and in 3 of the 18 non-CIC patients (16.7%); and the frequencies were significantly different ($p = 0.0061$) (Table 3b).

Discussion

Despite extensive diagnostic evaluation and numerous treatment guidelines,[1–4] a number of patients remain troubled by chronic and uncontrollable cough. Though asthmatic cough, gastro-esophageal reflux (GER)-associated cough, and postnasal drip (PND)-induced cough are recognized as major causes of chronic cough in western countries,[4] GER-associated cough and PND-induced cough are very rare in Japan.[7,8] Recently a prospective multicenter study revealed that atopic cough (AC), cough-variant asthma (CVA), and sinobronchial syndrome (SBS) are major causes of chronic cough in Japan.[7]

Diagnosing patients with intractable cough as having CIC[5,6] limits the management of disease in such patients; therefore, it is important to investigate how to appropriately address this problem and minimize the diagnosis of CIC, even if the major causes of chronic cough exhibit geographical variation.

Haque et al.[5] reported the median duration of CIC to be 72 months, but this duration ranges from 8 to 324 months. Therefore, it may be difficult to identify CIC as a homogenous clinical entity. Therefore, it is fascinating to investigate the CIC from a new perspective. Here, we explain the importance of environmental fungi such as BM fungi in investigating the disease in patients with chronic intractable cough.

There have been an increasing number of studies concerning the relationship between intractable allergic diseases and environmental fungi and these studies have attracted attention in the fields of otolaryngology[19] and dermatology.[20] However, these studies have been limited to allergic bronchopulmonary aspergillosis (ABPA)[21] and trichophyton-sensitized asthma[22] in the field of respirology.

We have previously reported cases of AC caused by a hypersensitivity to *Trichosporon asahii*,[23] *Pichia guilliermondii*,[24] *Streptomyces albus*,[25] and also reported the first case of nonasthmatic sputum eosinophilia caused by allergic reaction to a BM fungus (originally mislabeled as *Humicola fuscoatra*) in which the increase of eosinophils in the induced-sputum was established by repeated environmental surveys to be closely related to the appearance of BM fungi in the patient's house.[26] Furthermore, we have reported several cases of AC which were sensitized with BM fungi and successfully eradicated and treated with low-dose itraconazole[27] or oral cleansing with amphotericin B.[28]

Although only a limited number of the literature has documented infectious diseases caused by BM fungi, such as *Schizophyllum commune*,[29] the *Coprinus* species,[30] much of the literature reports the possible role of basidiospores as airborne allergens.[31,32]

From the results of our series of studies on patients with fungus-associated atopic cough,[23–26] we have focused on the possible role of BM as a fungal aeroallergen. Initially we performed pharyngeal swab cultures for the detection of fungi in 141 patients with chronic nonproductive cough and identified *Candida* and BM in 10.6% and 6.4% of all the examined patients, respectively.[33] Since BM fungi are rarely detected in the culture of pharyngeal swabs taken from non-coughers,[34] and the positive ratio of the immediate subcutaneous reaction for BM fungi in allergic airway diseases such as atopic cough (AC), cough-variant asthma (CVA), and cough-predominant asthma was significantly higher than that in non-coughers (unpublished data), we suspected that the positive culture results were not caused by an environmental fungal contamination. Therefore, we have hypothesized that BM fungi colonizing in the pharynx or lower respiratory tract plays an important role in allergic airway disorders.

Aspergillus is well known to be the cause of eumycetes. When culturing sputum for detection of eumycetes, it should be noted that although it requires only approximately 2 days for detecting *Aspergillus*, approximately 10

Table 2 Comparison of the characteristics between CIC and non-CIC patients.

Variables	CIC	Non-CIC	*p* Value
Median age, yr	59 (22–80)	51 (22–78)	0.2673
Gender, male:female	11:08	22:29	0.0714
Median duration of cough, mo	24 (8–720)	12 (8–480)	0.0292
Preceded by URTI, yes:no	2:10	3:37	0.3448
Median C5 (solution number)	3 (1–8)	4 (2–8)	0.0292
Median PC20 (mg/mL)	20 (5–20)	10 (0.078–20)	0.0416
Median FEV_1/FVC ratio	82 (60–100)	80 (71–99)	0.9999
Median reversibility	24 (−3.6 to 17.4)	24 (−6.5 to 15.2)	0.5381

Table 3a The frequencies of positive sputum culture for all fungi in 34 patients with chronic cough.

Basidiomycetous fungi	13
Candida albicans	9
Aspergillus fumigatus	5
Penicillium	5
Aspergillus niger	3
Aspergillus flavus	1

days are required for culturing BM. During the 10th annual meeting of the Japan Cough Research Society, it was found that several laboratories store the nutrient medium only for approximately 2 days. This renders the detection of BM impossible in the institutions that discard the culture medium after 2 days.

Thus, we proposed a new clinical disease concept termed fungus-associated chronic cough (FACC),[9] which entailed the following manifestations: (1) chronic cough; (2) the presence of environmental fungi, particularly basidiomycetous (BM) fungi, in the sputum; and (3) good clinical response to antifungal drugs. Because FACC shows clinical response to antifungal drugs, the participation in planning of the antifungal drugs may become a new attractive strategy in the treatment of chronic cough.

Our previous study has revealed that allergic fungal cough (AFC) is a type of FACC.[10] AFC is intractable and is characterized by sensitization with *B. adusta*, which is a basidiomycetous fungus. The clinical features in the 5 patients in our hospital diagnosed with AFC are as follows: (1) chronic intractable cough with a tickling sensation and a feeling of something being stuck in their throats, lasting for more than 8 weeks; (2) the presence of environmental fungi such as BM fungus, particularly, *B. adusta*, in the sputum; (3) positive reactions to inhalation bronchoprovocation test and/or lymphocyte stimulation test to the fungus; (4) clinical response to antifungal drugs requiring long duration (more than approximately 10 weeks) for complete remission of cough symptoms; and (5) frequent recurrence of cough.

If the new disease concept of AFC had not been devised, the clusters of 5 patients would have been diagnosed with chronic idiopathic cough (CIC). On the basis of these experiences, we investigated these patients for the clinical manifestations of AFC before diagnosing these patients with CIC. To assess the usefulness of diagnosing AFC in patients with CIC, we determined the incidence of CIC among our hospital patients, and the frequency of BM fungi in sputum samples collected from patients with CIC. We also determined whether or not a recognizable clinical pattern that distinguishes CIC from non-CIC exists.

Table 3b The frequencies of positive sputum culture for BM fungi in 34 patients with chronic cough.

Primary diagnosis			Obtained sampling no.	BM positive no.
CIC			16	10
Non-CIC	Cough-variant asthma		8	1
	Atopic cough		6	2
	Sinobronchial syndrome		3	0
	Cough-predominant asthma		1	0
	Others	GER	0	0
		Psychogenic	0	0

In this study, a diagnosis could not be achieved in 19 patients (27.1%); these patients were therefore assigned to CIC according to the Japanese Cough Research Society,[1] Japanese Respiratory Society,[2] and the American College of Chest Physicians (ACCP) evidence-based practice guidelines.[4] The results of this study conducted in our hospital demonstrate that CIC is not a rare condition. Except for the median duration, none of the clinical characteristics significantly differed between the CIC and the non-CIC patients. CIC patients had a significantly higher cough reflex sensitivity in response to capsaicin and lower bronchial responsiveness as compared to non-CIC patients. These results can be explained by the fact that the patients with non-CIC exhibited a relatively high incidence of increased bronchial responsiveness exhibited by conditions such as CVA and cough-predominant asthma and relatively low incidence of increased cough reflex sensitivity exhibited by conditions such as AC and GER. In other words, asthmatic cough, such as CVA and cough-predominant asthma, does not seem to be frequently encountered in patients with CIC.

It is remarkable that BM fungi were the most common species among the fungi identified in the sputum samples obtained from CIC patients and that the positive ratio of BM cultured from the sputa of CIC patients was significantly ($p = 0.0061$) higher than that of non-CIC patients.

From these findings, the existence of BM fungi in induced sputum may be one of the important factors to distinguish the clinical manifestation of CIC from that of non-CIC. Therefore, detecting BM fungi from the expectoration of the CIC patients may become a clue that leads to a part of success in the management of CIC.

Conflict of interest

The authors declare that they have no competing interests that might be perceived to influence the results and discussion reported in the present manuscript.

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